REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office Action dated March 13, 2003 are respectfully requested. A separate petition for a 2-month extension of time accompanies this amendment. Claims 1-11 and 13-15 are currently under examination.

In view of the Examiner's earlier restriction requirement, Applicants retain the right to present claims 12, 16 and 17 in divisional applications.

I. Amendments

Claim 1 has been amended to to recite that the bloodstream levels of 2',-5'-oligoadenylate synthetase are stimulated above the level of of 2',-5'-oligoadenylate synthetase present prior to treatment. Support for the amendment may be found on at least page 13, lines 18-19 of the specification.

Claims 4-10 have been amended to delete the time period for administration of the composition. Claims 11 and 13 were amended to clarify that the composition is formulated to avoid the tunica mucosa oris.

No new matter has been added by this amendment.

II. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-11 and 13 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claims 1 was rejected as being indefinite for reciting "an oral-delivery composition" and "an amount effective to stimulate bloodstream levels of 2',-5'-oligoadenylate synthetase." The Examiner asserts that it is not clear whether "oral-delivery" intends a particular form or physical property or an intended use, and that it is not clear to what degree synthetase levels would need to be stimulated in order to define clearly the effective amount being claimed. The Examiner also asserts that since

both serum levels and PBMC levels are disclosed, it is not clear what is intended by "bloodstream levels."

Claim 1 has been amended to recite that bloodstream levels of 2',-5'-oligoadenylate synthetase are stimulated above the level of of 2',-5'-oligoadenylate synthetase present prior to treatment, thereby making it clear to what degree synthetase levels need to be stimulated to clearly define the effective amount being claimed. As shown in Tables 3-6 on pages 16-20 of the specification, the level of 2',-5'-oligoadenylate synthetase may increase in the serum or PBMC or both.

The term "bloodstream levels" has been replaced with "serum levels," thereby obviating the rejection with respect to the term "bloodstream levels."

"An oral-delivery composition" intends a particular form or physical property of the claimed composition. Such forms and physical properties of oral-delivery compositions are described on page 12, lines 1-20 of the specification.

Claim 2 was rejected as being indefinite for not being clear as to whether the claim intends to recite the presence of additional IFN-tau, in addition to the IFN-tau recited in claim 1.

Claim 2 was amended to remove the term "further" as suggested by the Examiner.

Claims 4-10 were rejected as being indefinite for reciting the term "Units/day." Claims 4-10 have been amended to delete the time period for administration of the composition.

Claims 11 and 13 were rejected as being indefinite for reciting that the dosage avoids the tunica mucosa oris because it is not clear whether the cited terminology intends to convey a property or a route of administration. Claims 11 and 13 have been amended to state that the dosage is formulated to avoid the tunica mucosa oris. Such formulations are described, for example, on page 12, lines 11-16 of the specification.

Accordingly, Applicants submit that the presently pending claims satisfy the requirements of 35 U.S.C. §112, second paragraph.

III. Rejection under 35 U.S.C. §§102(e)/103(a)

Claims 1-11 and 13-15 were rejected under 35 U.S.C. §102(e) as being anticipated by, or in the alternative, under 35 U.S.C. §102(e) as being obvious over Soos *et al.* (U.S. Patent No. 6,372,206).

This rejection is respectfully traversed in view of the foregoing claim amendments and following remarks.

A. The Invention

The present invention, as embodied in claim 1, is directed to an oral-delivery composition for use in treating HCV in a HCV-infected patient. The composition includes ovine IFN-τ in a dosage effective to stimulate bloodstream levels of 2', 5'-oligoadenylate synthetase synthetase (OAS) relative to bloodstream levels of of OAS prior to treatment.

The advantages of this invention include a) the convenience of a composition prepared for oral delivery, particularly in situations in which frequent doses are necessary, and the resulting improved patient compliance; b) the *in vivo* efficacy of the oral-delivered IFN-τ in increasing OAS levels, which is considered responsible, at least in part, for the antiviral state established in cells and plays a role in the elimination of HCV (page 10, lines 24-25 of the specification).

The advantages of the invention were unexpected for the following reasons, and as discussed further below:

First, there was no reasonable expectation that a composition formulated for oral-delivery of ovine IFN-τ would actually be effective in increasing the levels of blood OAS or blocking the development or the recurrence of HCV in a human patient. Prior to this work, only mouse IFN-τ had been known to be effective in mice.

Second, there was no reasonable expectation that the low cytotoxicity of IFN-τ observed *in vitro*, or when administered by injection, would be retained by oral administration when administered in dosages high enough to increase bloodstream OAS levels or as high as those recited in claims 4-10.

Third, as recited in claims 2, 3, 11 and 13, the composition is formulated to avoid the tunica mucosa oris. This formulation diminishes antibody formation against IFN-τ compared to IFN-τ absorbed through the oral mucosal membrane, particularly in the case of chronic administrations of IFN-τ.

B. The Cited Art

Soos *et al.* teaches that oral administration of IFN-τ is effective to treat autoimmune disorders , numerous cell proliferative disorders and a long list of viral diseases at dosage concentrations of between 10^5 to 10^8 units per day.

Nowhere does Soos *et al.* show or suggest the use of high dosage compositions (particularly the dosage levels recited in claims 4-10) which are capable of increasing the blood OAS levels for the treatment of HCV. Nor does Soos *et al.* provide data relating to the prevention or treatment of HCV. Soos *et al.* also fails to provide data on the levels of OAS in the bloodstream following oral administration which is indicative of successful HCV treatment. Finally, Soos *et al.* does not disclose or recognize a composition formulation capable of avoiding the tunica mucosa oris.

C. Analysis

For a prior art reference to be anticipating under 35 U.S.C. §102, it must teach "each and every" element of the claimed invention. *In re Bond,* 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). "Anticipation requires identity of invention: the claimed invention, as described in appropriately construed claims, must be the same as that of the reference, in order to anticipate." *Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc.,* 33 USPQ2d 1496 (Fed. Cir. 1995).

Applicants submit that the cited reference does not meet the legal standard of anticipation. There is no disclosure of IFN-τ dosages effective to increase bloodstream OAS levels or to treat HCV. Nor is there a disclosure of the high dosage levels recited in claims 4-10. Furthermore, there is no disclosure or recognition that any of the formulations disclosed in Soos *et al.* would be effective to avoid the tunica mucosa oris. Thus, the reference does not contain each and every element of the claims, and therefore cannot anticipate the claims.

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the invention should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). The Examiner has shown neither the suggestion nor the expectation of success in any cited prior art reference.

Motivation. The cited art does not suggest an oral-delivery composition that should be administered at high dosage amounts effective to increase the blood level of OAS which would be effective to treat HCV. Soos *et al.* is directed to amounts of oral IFN-τ which do not have any toxic side effects. The dosages disclosed in the application show no ability to increase OAS levels or treat HCV.

Reasonable likelihood of success. There are two reasons why the cited art does not suggest a reasonable likelihood that IFN-τ would be effective when administered orally at levels high enough to produce OAS increases in blood and treat HCV, as discussed more fuuly below.

Oral administration of high dosage levels of proteins The cited art provides no expectation that IFN-τ, when administered orally at high dosage levels, would be effective in treating a disease condition responsive to IFN-τ, or that IFN-τ would retain its unique properties when administered orally at levels high enough to produce these OAS level increases.

The general belief in the art is that the efficacy of orally-administered protein-based medicaments is highly unpredictable, due in large part to the large number of proteases and peptidases that an ingested peptide encounters during passage through the intestinal tract, and to the likelihood of poor absorption in the gastrointestinal tract. Woodley (1994) Crit. Reviews in Therapeutic Drug Carrier Systems 11:61-95, discusses the "enzyme barrier" presented by the estimated forty or more peptidases and proteases that an orally administered peptide may encounter during its passage throught the GI tract. Banga, Therapeutic Peptides and Proteins, Technomic Publishing, Lancaster PA (1995), pp. 217-244, outlines the various enzymatic and physical barriers to oral bioavailability. The Examiner has not provided any evidence which would indicate that IFN-τ would be an exception to the unpredictable nature of oral, high dosage level administration of proteins.

Unexpected Results

The cited references do not suggest the possibility of achieving the results of the invention. The test of obviousness is whether the invention as a whole would have been obvious, including the nature of the results obtained (e.g., *Novo Industri A/S v. Travenol* 215 USPQ 412; *In re Papesch* 137 USPQ 43; and *In re Yates* 211 USPQ 1149.)

Not only was orally-administered IFN-τ effective at treating a disease benefiting from IFN-τ treatment (HCV), but the formulations were effective to increase the level of OAS in bloodstream. With regard to claims 11 and 13, compositions that are formulated to avoid the tunica mucosa oris resulted in unexpected advantages relative to treatment with IFN-τ compositions that are not formulated in such a manner. For example, orally-administered IFN-τ that is directly absorbed through the stomach mucosal membrane diminishes antibody formation against IFN-τ compared to IFN-τabsorbed through the oral mucosal membrane. This is beneficial because the orally-administered IFNτ is therefore less likely to be rendered ineffective by a host immune response (*i.e.*, desensitization to the treatment and/or dose level is significantly decreased), and the individual receiving the treatment is less likely to suffer adverse side effects as a result of such an immune response."

Nothing in the cited reference suggests the unexpected advantage of reduced anti-IFNτ antibodies in the bloodstream following direct absorption through the stomach mucosal membrane, as opposed to absorption through the oral mucosal membrane. This unexpectedly reduced subject immune response has numerous advantages for protein-based therapeutics, particularly in prolonged therapeutic regimes.

Enablement

The Applicants submit that a reference relied upon to support a rejection under 35 U.S.C. §102 or §103 must provide an enabling disclosure, i.e. they must place the claimed invention in the possession of the public. *In re Payne*, 203 USPQ 245, 255 (CCPA 1979). The cited reference does not place oral delivery compositions comprising IFN-τ that are effective to treat HCV into the possession of the public.

In the present case, the issue is "Does the disclosure of Soos *et al.* describe the claimed invention with sufficient specificity to put the public in possession of the invention?"

Applicants submit that Soos *et al.* fails to meet this legal standard and does not disclose the claimed invention with sufficient specificity to put the public in possession of the invention. As noted above, the "laundry list" of various diseases, cancers and infections recited in Soos *et al.* (column 4, lines 40-60) includes numerous conditions known to not be effectively treated with IFN-τ at the dosage levels disclosed. Given that there is no indication in the reference that all of the conditions listed in Soos *et al.* are effectively treated by the dosage levels disclosed in Soos *et al.*, how can it be asserted that the claimed method of treating HCV is disclosed by Soos *et al.*, when neither the public nor one of skill in the art knows which, if any, of the dosage levels will effectively increase bloodstream OAS levels or treat HCV?

The mere naming of a condition in a reference naming a myriad of conditions, without more, cannot constitute a description of an effective treatment for that condition by the disclosed compound. In *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1973, claims to a compound useful for treating Parkinson's disease were

rejected as anticipated by a reference that disclosed the claimed compound but that failed to describe a synthetic method suitable for preparing the compound. A method for preparing the compounds was not developed until a date later than that of the reference.

In reversing the Examiner's rejection of the claims, the court that a reference's listing of specific compounds within the scope of the claimed compound constituted nothing more than mere speculation about their potential or theoretical existence and, hence, was not a description of the compounds within the meaning of §102. *Id. at* 543, 179 USPQ 421, 425.

Similarly, in the present case, Soos *et al.* lists dozens of conditions and various ranges of IFN-τ as therapeutic compositions. Many of the conditions listed are known to not be effectively treated by IFN-τ at the dosage levels indicated. Likewise, it cannot be known which, if any, of the listed IFN-τ dosage levels might be effective to treat HCV, since the mere listing of the compound ranges is nothing more than speculation about their usefulness in treating HCV and dozens of other conditions. Thus, the speculative disclosure of Soos *et al.* of HCV as one of dozens of possible candidates to include for treatment with IFN-τ cannot be said to place the possession of the claimed invention.

Hindsight

Applicants believe that the Examiner is basing the rejection on the idea that it would have been "obvious to try" higher dosage levels of IFN-τ such that they increase the blood level of OAS and effectively treat HCV. The obvious to try criterion, however, is insufficient to make an invention obvious. *In re Dow Chemical*, 5 USPQ2d 1529 (Fed. Cir. 1988), *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988). The Court's holding is apt:

"What would have been obvious to try would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art either gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Id.* at 1681.

Hence, even if it is "obvious to try" higher dosage levels of IFN-τ such that they increase the blood level of OAS and effectively treat HCV, one of ordinary skill in the art would not have had a reasonable expectation of success.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §102(e)/§103(a).

IV. Conclusion

In view of the above remarks, the applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4405.

Respectfully submitted,
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